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to develop better measures of MDMA toxicity, and to more accurately determine how much drug is used and in what circumstances.

If conducted with large enough groups of MDMA users and control subjects, both drug naïve and matched for poly-drug use, longitudinal studies could also help identify risk and protective factors for drug use and the deficits that result from continuing exposure to MDMA. The identification of significant risk and protective factors would greatly aid the development of efficacious prevention and rehabilitation approaches. Data from longitudinal studies would also help establish associations between MDMA use and behavioral impairments that researchers have observed in the majority of studies.

Longitudinal designs may enable researchers to determine how long such impairments last, whether they are progressive, and if deficits become more evident as MDMA users move into middle and late adulthood or experience other age-related neurologic disorders. Questions about the reversibility of impairments, a concern given the data seen in animal studies and even in some human studies, could also be addressed by such designs. Longitudinal studies should also provide data on critical patterns of MDMA use that may be more or less likely to cause impairments, and can help to determine whether simultaneous abuse of other drugs plays a role in causing behavioral and cognitive damage.

Along with such studies, researchers need better tools to assess neurotoxicity in human MDMA users and to measure changes of neuronal integrity and possible recovery over time. With such tools, investigators may also be able to address important mechanistic questions, such as how damage to the serotonin system leads to behavioral and cognitive changes, how the brain responds to and compensates for serotonergic damage, and why the dopaminergic system seems to escape lasting damage from MDMA. Such studies might then lead to the development and validation of methods for promoting recovery from MDMA-induced neurotoxicity.

There is also a need for more studies looking at the long-term effects of poly-drug abuse. Such studies will require new analytical tools for detecting multiple drugs of abuse simultaneously in biological samples and for more accurately assessing drug use histories, including the combination and sequencing of drugs used.

There are little data available on whether addiction, dependence or tolerance develops with continued use of MDMA. Though the data from animal studies support this possibility, more studies are needed in humans to determine the degree of abuse liability for this drug and to help develop treatments specific for reducing MDMA addiction. Along the same lines, researchers at this meeting stressed again that there are little data on numbers of drug treatment patients who have used MDMA or who have sought treatment because of MDMA abuse.

Another scientific gap idenitfied at the scientific conference concerns the development of methods for tracking so-called hidden populations of MDMA users; that is, those who don't go to dance clubs or raves, where the majority of volunteer recruiting occurs. At the same time, researchers also stressed the need to better understand the youth party culture that seems to actively promote MDMA use through the use of in-house drug dealers and marketing messages delivered through music and by pop icons.

There is a need to foster interdisciplinary research and dialogue that links epidemiological, ethnographic, clinical and laboratory studies. As this report shows, there is much overlap between these separate fields, and undoubtedly, this area of investigation could benefit from better coordination between disciplines. There is also a need to link local, regional, national, and international supply-side intelligence with demand-side epidemiological and ethnographic research.

Prevention efforts cannot be universal but must be targeted at different groups that use MDMA, particularly since MDMA appears to be a drug whose use is sensitive to and intimately linked with social context and networks. In particular, there is a need to integrate local research, services, prevention and intervention efforts to provide targeted, shared messages. The conference speakers recommended that there be a new focus within youth networks and adult education programs to counter the perception that MDMA is much safer than other drugs. The use of youth-led advocacy and drug prevention programs seems particularly promising for reducing MDMA use among adolescents and young adults.

SOURCE: Much of this report is based on a scientific conference—*MDMA/Ecstasy Research: Advances, Challenges, Future Directions*—that was sponsored by the *National Institute on Drug Abuse (NIDA)* and the *National Institutes of Health* and held July 19-20, 2001. Information in this report was supplemented by an exhaustive review of the extensive published scientific literature on MDMA, particularly that which has appeared in scientific and medical journals during the past five years.

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Ecstasy: What We Know and Don't Know About MDMA - A Scientific Review

A number of our Nation's best monitoring mechanisms have detected an alarming increase in the popularity of MDMA (3,4-methylenedioxymethamphetamine), particularly among young Americans. Unfortunately, myths abound about both the acute effects and long-term consequences of this drug, also known as "Ecstasy," with many young people believing that MDMA is safe, offering nothing but a pleasant high for the $25 cost of a single tablet. But MDMA is not new to the scientific community, with many laboratories beginning their investigations of this drug in the mid 1980s, and the picture emerging from their efforts paints a much different image of this drug, one that is far from benign.

This report, *Ecstasy: What We Know and Don't Know About MDMA*, represents a scientific review of what research has discovered about how this drug works in the brain and what requires further study to fully understand the consequences of using this illicit substance. This report discusses what scientists know and don't know about MDMA's acute effects on the brain and behavior from laboratory studies in both animals and humans. The report also reviews the long-term effects on the brain, again in both laboratory animals and humans, as well as long-term behavioral consequences detected in chronic MDMA users.

MDMA, a relatively simple chemical belonging to the amphetamine family of compounds, has properties of both stimulants and hallucinogens. While MDMA does not cause true hallucinations, many people have reported distorted time and perception while under the influence of this drug. The vast majority of people take MDMA orally, and its effects last approximately four to six hours. Many users will "bump" the drug, taking a second dose when the effects of the initial dose begin to fade. The typical dose is between one and two tablets, with each containing approximately 60-120 milligrams of MDMA. However, tablets of what users call Ecstasy often contain not only MDMA but a number of other drugs, including methamphetamine, caffeine, dextromethorphan, ephedrine, and cocaine.

One of the more alarming facts about MDMA is that despite its known detrimental effects, there are increasing numbers of students and young adults who continue to use the drug. Results from the 2000 Monitoring the Future survey indicate that MDMA use increased among students in the 12th, 10th, and 8th grades. African Americans show considerably lower rates of MDMA use than do either whites or Hispanics. The recent CEWG data showed a large increase in use among Hispanics that may represent an important change.

Effects of Acute Doses of MDMA

MDMA works in the brain by increasing the activity levels of at least three neurotransmitters: serotonin, dopamine, and norepinepherine. Much like other amphetamines, MDMA causes these neurotransmitters to be released from their storage sites in neurons, increasing brain activity. Compared to the potent stimulant methamphetamine, MDMA triggers a larger increase in serotonin and a smaller increase in dopamine. Serotonin is a major neurotransmitter involved in regulating mood, sleep, pain, emotion, and appetite, as well as other behaviors. By releasing large amounts of serotonin, and also interfering with its synthesis, MDMA leads to a significant depletion of this important neurotransmitter. As a result, it takes the human brain a significant amount of time to rebuild the store of serotonin needed to perform important physiological and psychological functions.

One hypothesis to explain the long-lasting neurotoxicity of MDMA on serotonergic systems is that MDMA induces both oxidative and metabolic stress in serotonin neurons that, in turn, adversely affect the ability of these neurons to produce serotonin. Support for this hypothesis comes from a variety of studies, including those showing that MDMA perturbs the activity of various antioxidant enzymes; artificially boosting the levels of these enzymes reduces MDMA's effects on serotonin and dopamine neurons. Also, stress appears to increase the oxidative damage caused by MDMA.

It has been difficult to study the effects of MDMA in humans under controlled conditions, and virtually impossible until recently to conduct simultaneous neurochemical studies. However, several groups of researchers have chosen to study the behavioral pharmacology of MDMA in various animal species, showing that MDMA and related compounds produce a unique behavioral profile in rodents. Studies in non-human primates suggests that acute doses of MDMA may have subtle effects on higher cognitive functions, including memory and learning. Other experiments in laboratory animals suggest that MDMA is a drug that humans are likely to abuse, and that humans may develop tolerance to MDMA's reinforcing effects. Limited studies in humans have shown that MDMA negatively impacts short-term performance on a variety of measures of cognitive ability.

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Controlled studies in humans have shown that MDMA has potent effects on the cardiovascular system and on the body's ability to regulate its internal temperature. Of great concern is MDMA's adverse effect on the pumping efficiency of the heart - in the presence of MDMA, increased physical activity increases heart rate significantly, but the heart does not respond in its normal manner, which is to increase the efficiency with which it pumps blood. Since MDMA use is often associated with sustained, strenuous activity, such as dancing, MDMA's effects on the heart could increase the risk of heart damage or other cardiovascular complications in susceptible individuals.

Pharmacokinectic studies have shown that MDMA is rapidly absorbed into the human blood stream, but once in the body the metabolites of MDMA inhibit MDMA metabolism. As a result, subsequent doses of the drug produce unexpectedly high blood levels, which could worsen the cardiovascular and other adverse effects of this drug without increasing its "pleasurable" effects, which tend to peak about two hours after taking an initial dose. MDMA interferes with the metabolism of other drugs, including some of the adulterants in MDMA tablets.

Long-Term Consequences of MDMA: Neurochemical and Developmental

Acute doses of MDMA produce marked changes in both dopamine and serotonin systems within the brain. Though the changes in dopaminergic neurons appear transient, the data suggest that the changes in the serotonergic system are longer-lasting. In addition, examinations of more global brain function have shown that the effects of acute doses of MDMA extend to regions of the brain that are thought to be involved in higher thought processes. These findings have raised concern about possible long-term effects on both infrequent and regular users of MDMA.

Several groups have shown that exposure to MDMA rapidly and persistently destroys a key marker of serotonergic function in regions known to have a high density of serotonin neurons, including the striatum and cortex. More detailed examination of this structural damage shows that MDMA appears to prune, or reduce in number, serotonin axons and axon terminals. Eighteen months after a short course of MDMA, investigators found that some brain regions had substantial loss of serotonin axon terminals, while a few others had more serotonin axon terminals. This pattern is a hallmark of axon pruning, since nerve cells will often grow replacement terminals upstream of the damaged terminals. These results, then, are evidence not only of MDMA's neurotoxicity, but of the brain attempting to rewire the serotonin system after damage.

Since younger brains may have an increased susceptibility to the neurotoxic effects of MDMA, it may be that the youngest, fastest developing brains - those of a developing fetus - could be particularly vulnerable to the effects of this apparent serotonin neurotoxin. Since most MDMA users are young and in their reproductive years, it is possible that some female users may take MDMA when they are pregnant, either inadvertently or intentionally, because of the misperception that it is a safe drug. Studies in animals have shown that MDMA has little effect on the physical development of the young brain. Behavioral and cognitive studies in laboratory animals, however, have identified significant adverse cognitive effects from pre and neonatal exposure to MDMA. This effect was not due to serotonergic neurotoxicity; the mechanisms underlying the development of these cognitive deficits are not known yet. Though the rodent experiments have predictive value, it is not known whether human fetuses exposed to MDMA when their mothers abuse the drug will develop persistent and learning memory deficits.

Long-Term Functional Consequences of MDMA: Behavioral, Mood, Psychiatric, and Cognitive

Because MDMA produces long-term deficits in serotonin function, and because serotonin function has been implicated in the etiology of many psychiatric disorders including depression and anxiety, investigators have suspected that MDMA users may experience more psychopathology than non-users. Indeed, a number of investigators have found that heavy MDMA users experience a constellation of psychiatric changes, scoring significantly higher on measures of obsessive traits, anxiety, paranoid thoughts, and disturbed sleep, among others. One study, aimed at developing reliable measures of diagnosing substance abuse disorders, found that 43 percent of MDMA users met DSM-IV criteria for dependence and 34 percent met the criteria for abuse of MDMA.

There is a large and growing body of evidence from a variety of studies with humans that MDMA use can have long-lasting effects on memory. None of these studies are perfect, as they all have methodological concerns such as concurrent use of other drugs (it is apparently impossible to find but a few MDMA users who do not use other illicit substances, particularly marijuana). In addition, results vary with the assessment used. Nonetheless, the general finding that emerges across all of the studies is that MDMA does impact memory abilities in ways that could adversely affect normal functioning on every day tasks. Moreover, the relationship between memory problems and MDMA use appears to have a dose-dependent relationship, that is, the more MDMA used, the greater the deficit.

Given that numerous studies have shown that the serotonin deficits caused by MDMA are persistent, lasting at least seven years in one study of nonhuman primates, it is important to determine if the psychological and memory deficits associated with even moderate use of MDMA recover after some period of time. This is a particularly important issue with MDMA because of the relatively young age of the majority of people who abuse this drug. So far, the majority of studies have focused on MDMA

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users who have been abstinent for a period of a few weeks to a few months - longer-term studies have been planned or are underway - and these have shown that the adverse psychiatric and cognitive changes associated with MDMA use are persistent.

In attempting to answer the question of whether MDMA causes permanent damage to human memory abilities, there is no one study that provides a resounding, definitive yes. To be sure, no study provides any evidence that MDMA is a beneficial drug or even that it is safe when taken in moderation. In fact taking MDMA at any dose carries with it the risk of inducing physiological, psychological, and cognitive damage in vulnerable users. Clearly, there is still room to debate the exact nature of the deficits produced by MDMA use. Nevertheless, based on the results from the overwhelming majority of studies conducted so far, the data show that MDMA can be harmful to human health.

Methodological Issues

As much as the data collected so far largely supports the proposition that MDMA damages the serotonin system in the brain and produces long-lasting behavioral deficits, researchers agree that methodological issues, such as limited sample size and difficulties controlling for the possible influence of other illicit substances, have made it difficult to move beyond generalities and unequivocally prove a cause and effect relationship between MDMA use and specific cognitive or psychological damage in humans.

All of the studies reviewed in this report have relied on self-referred MDMA users, recruited through targeted sampling techniques by advertising for volunteers or through word-of-mouth. This introduces an unknown bias into each study since it is possible that such self-referrers are not representative of MDMA users as a whole. There is also the problem of verifying that what users report as Ecstasy is, in fact, solely MDMA. In addition, it is impossible to verify self-reports of past drug use beyond a certain period of time, making it difficult at best to accurately control for prior drug use.

Since there seem to be few, if any, young people who use MDMA without also abusing other drugs, this will continue to be a confounding factor in future studies. Some investigators have tried to accommodate this problem by using a control group comprising individuals who have never used MDMA but who otherwise have closely matched histories of using other drugs of abuse. This type of control has not been used universally, however, and even when it is, it may be difficult to closely match users and controls for prior drug use, as well as on other demographic details such as educational level and age.

Self-reporting also means that it is not possible to determine with complete confidence or accuracy how much a person has consumed, either on a particular occasion or over a lifetime of use. This uncertainty arises for two reasons: MDMA content is not constant across all tablets, and user memory of how much and how often a person took MDMA over many years is far from reliable.

Ideally, researchers would like to be able to study MDMA's effects in drug-naïve humans, and indeed, a limited number of groups in Europe have received approval from the appropriate governmental regulatory agencies and institutional review boards to conduct what would essentially be Phase I safety trials with MDMA in a limited number of humans. However, there is little likelihood of studying the effects of MDMA on large numbers of drug-naïve volunteers. An alternative might be to conduct longitudinal, controlled prospective studies, in which current MDMA users and controls of non-MDMA users are followed for many years to observe changes from some defined baseline.

Challenges and Future Directions

Though the data presented at this conference and in the literature support the hypothesis that MDMA produces acute behavioral and physiological effects, there is still more to be determined about factors that precipitate severe acute toxicity. For example, are there predisposing genetic factors that increase the risk for acute toxicity? Is overall health status important? Which organs and systems are the primary targets of MDMA toxicity? Are interactions with other drugs important? Does MDMA use lead to tolerance, withdrawal, and craving?

Because MDMA is not the only drug taken by young adults, there is a need for more characterization of interactions between these substances and a determination of how those drug interactions may influence acute toxicity. Is the practice of "bumping" or taking sequential doses of MDMA particularly dangerous? How do individual genetic factors influence MDMA metabolism and drug interactions?

One critical piece of missing data is the incidence of acute toxicity among MDMA users. Assembling this database will require improved emergency room reporting of MDMA-associated incidents. In addition, data do not yet exist on the number of people seeking treatment for MDMA-related dependence and behavioral or psychological problems.

One of the key concerns raised at the meeting was the lack of longitudinal studies designed to follow MDMA users, both as they continue to use the drug and after they have stopped using it. Such studies may provide important insight into how age and length of use affect MDMA's acute and long-term neurochemical toxicity. In addition, such studies would allow researchers to determine if deficits appear later in life, long after use stops, or if adverse effects diminish over time. Such studies, if designed with regular assessment intervals, might also allow researchers

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